

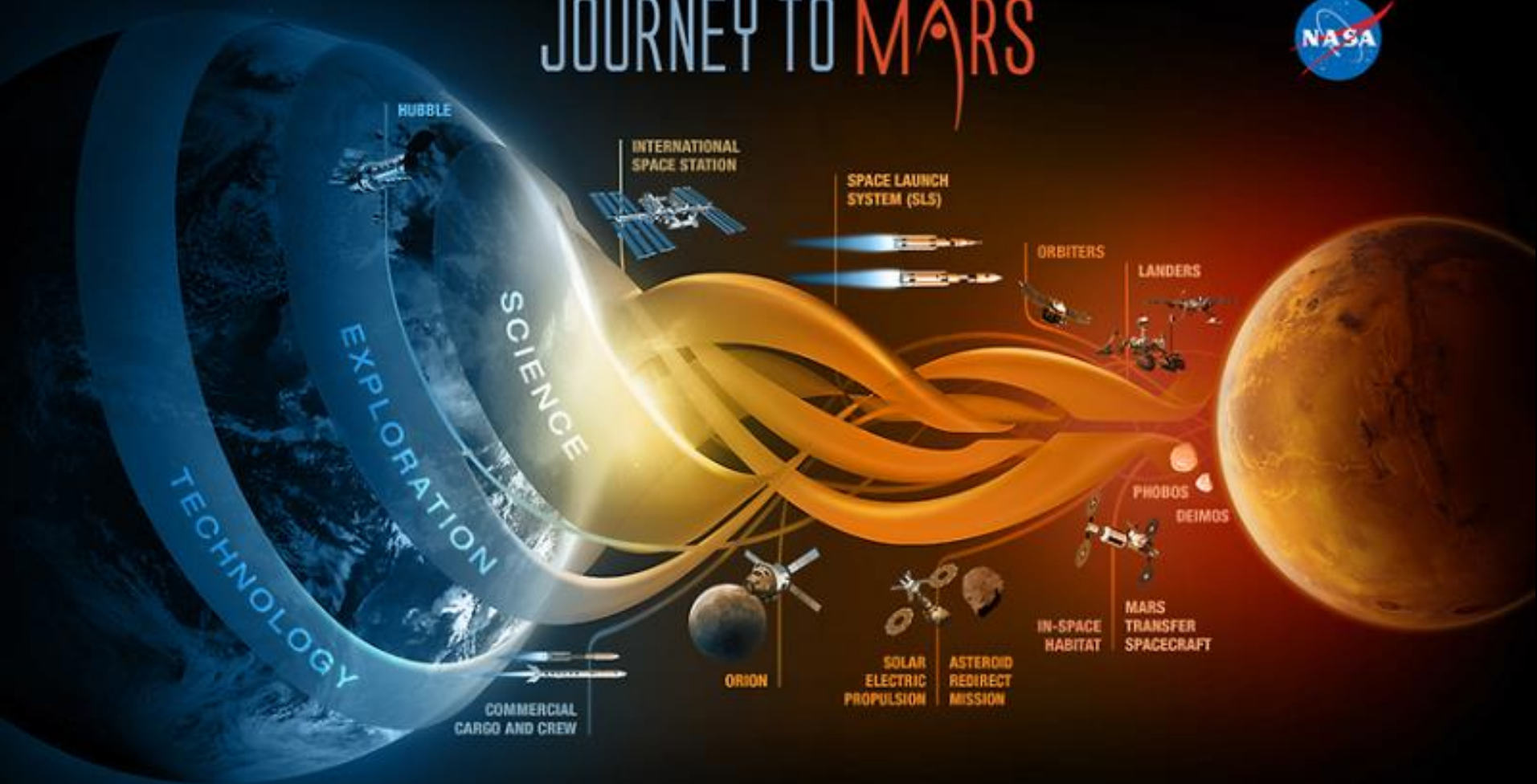
Immune Dysregulation Persists during Spaceflight: Case Study of an ISS Astronaut

Clinical and Research Findings



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JOURNEY TO MARS



Spaceflight Effects on Human Physiology

Dysregulation of the
immune system

Fluid Redistribution to
upper body

Plasma volume
decreases, anemia

Elevated radiation
may increase
cancer risk



Otoliths in inner
ear respond
differently, eyes
become main
way to sense
motion

Muscle and bone
weakening

Elevated kidney stone
risk



RADIATION

**MICROBES
INCREASE
VIRULENCE**

STRESS

MICROGRAVITY

**DISRUPTED
CIRCADIAN
RHYTHMS**

ISOLATION

**REDUCED
IMMUNE CELL
FUNCTION**

**ALTERED
CYTOKINE
BALANCE**

**Th1/
Th2**

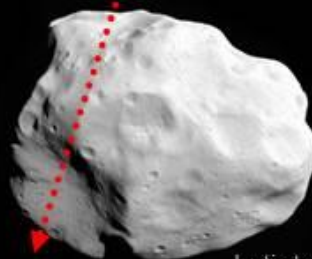
**LATENT VIRUS
REACTIVATION**

INCIDENCE?



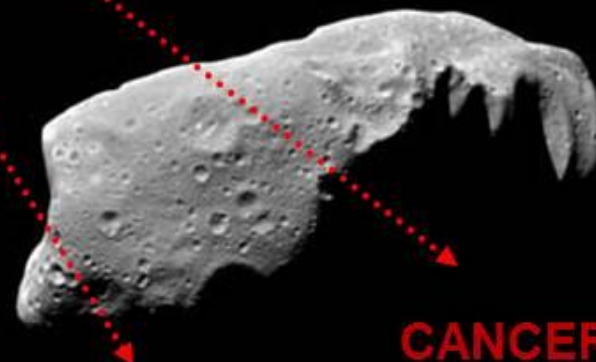
Eros

INFECTION?



Lutetia

HYPERSENSITIVITY?



Ida

CANCER?

AUTOIMMUNITY?

Applied Immunology

Skylab Data - 1973

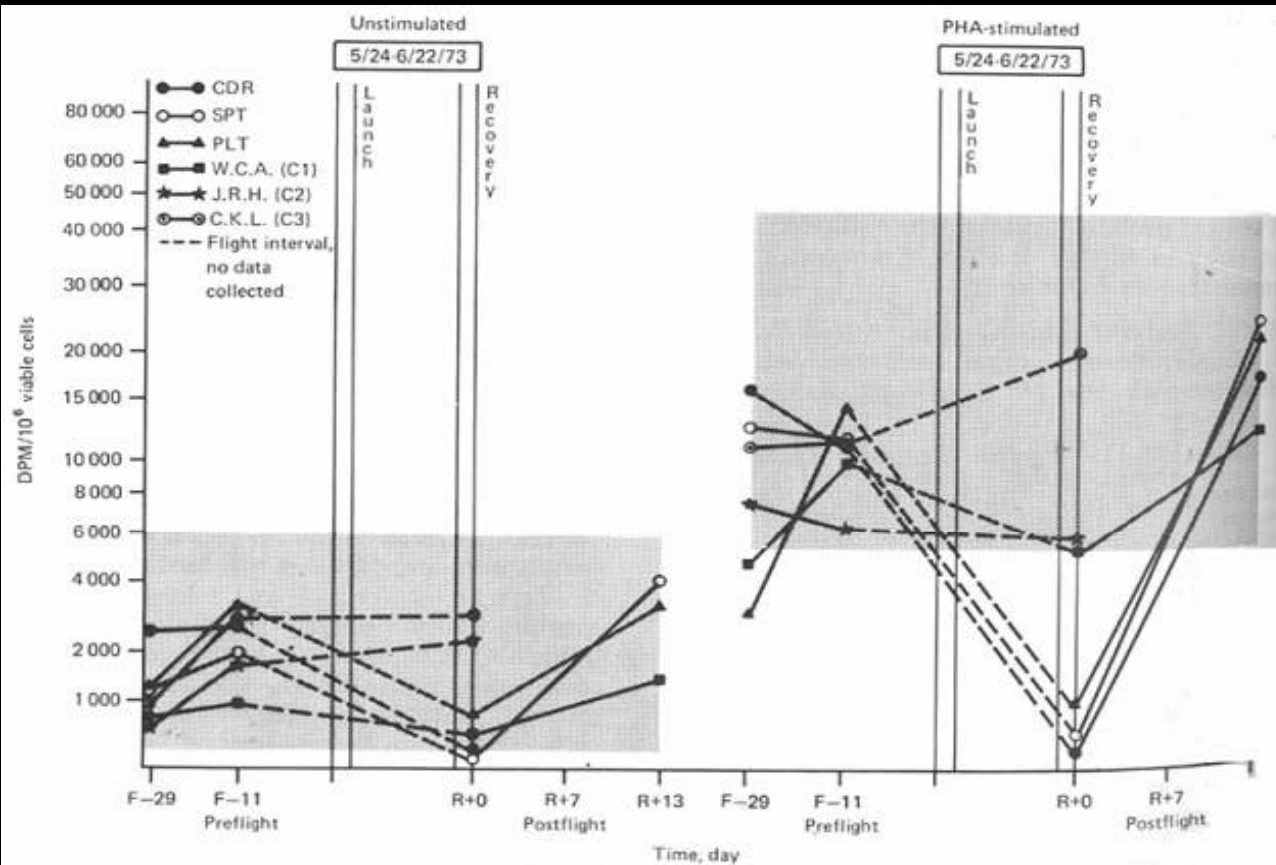


FIGURE 28-1a.—RNA synthesis rates in lymphocytes, cultured with and without PHA, obtained from the Skylab crews and control groups. The cells were pulsed with ³H-uridine at 23 h and harvested at 24 h after initiation of the cultures.



Summary of pre-ISS Evidence



In-flight cell culture

-Intracellular signaling, cytoskeleton rearrangement, microtubule organizing center orientation, generalized proliferative responses all altered during flight.

Reactivation of latent herpesviruses

-EBV, CMV, VZV reactivation during flight
-Infectious VZV particles secreted in saliva

Short duration

Long duration

Humoral immunity

-Immunization with antigen generates normal antibody response during flight (MIR-18)

Reduced cell mediated immunity

-CMI Multitest, common recall antigens, long duration flight

Post-flight observations

-Altered circulating leukocyte distribution
-Altered cytokine production patterns (secreted, intracellular, Th1/Th2)
-Decreased NK cell function
-Decreased granulocyte function
-Decreased T cell function*
-Altered immunoglobulin levels
-Latent viral reactivation
-Altered virus-specific immunity
-Expression of EBV IE/late genes*
-Altered neuroendocrine responses

*Post-flight observations differ between long vs. short duration space flight.



Samples - Timepoints

ISS Sample Types:

- Blood
- Saliva (Liquid)
- Saliva (Dry)
- Urine
- Health Survey



ISS Sample Schedule:



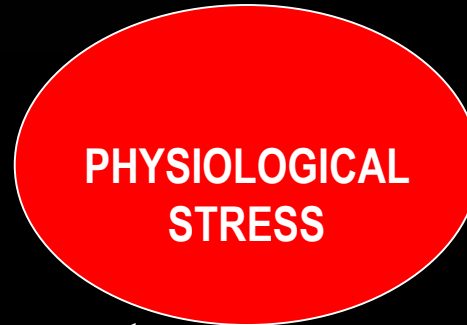


Assays



JSC Immunology Laboratory

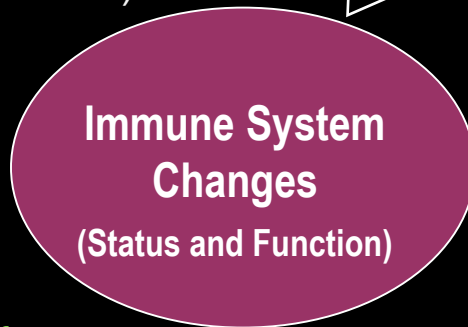
- Leukocyte subsets
- Intracellular cytokine profiles (4hr culture)
- T cell function (24h culture)
- Mitogen-stimulated cytokine profiles (48h culture)



- Stress hormone levels
- Circadian rhythm alignment

JSC Microbiology Laboratory

- Latent herpesvirus reactivation (saliva/urine)



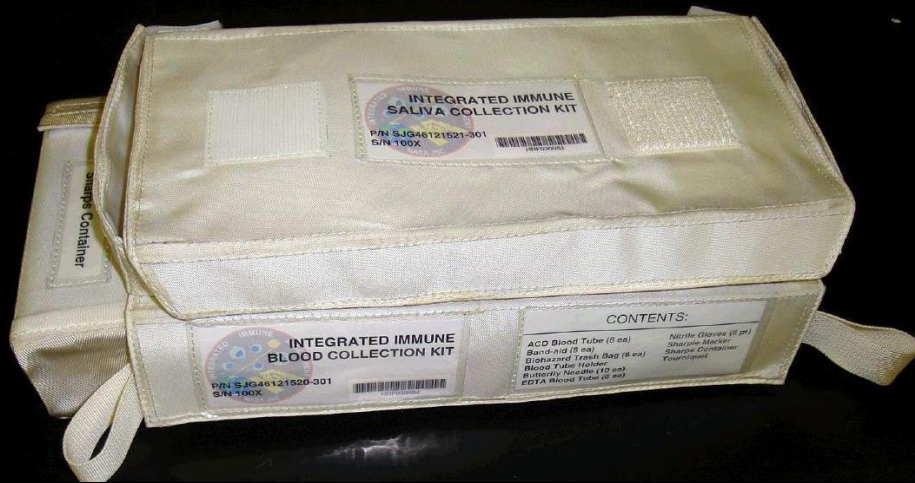
Mercer University

- Plasma cytokine balance
- Leukocyte cytokine RNA

Microgen Laboratories

- Virus specific T cell number
- Virus specific T cell function

Flight Hardware





Integrated Immune – Conclusions

'n' = 22 ISS Astronauts

Peripheral leukocyte distribution, T cell function, mitogen-stimulated cytokine profiles are all persistently dysregulated for the duration of a 6-month ISS mission.

Appears to be a pan-suppression of adaptive function, including viral specific T cells.

Latent herpesviruses, including VZV, persistently reactivate for the duration of a 6-month ISS mission.

Circadian misalignment occurs, difficult to regain a 'normal' circadian rhythm.
(Sleep meds most commonly prescribed Rx)

Clinical Incidence onboard ISS?

- A definitive tabulation in the literature is lacking, although various NASA activities have created incidence numbers (Clinical Finding Forms, etc.)
- Inability to confirm diagnoses
- Restricted to electronic examination
- Treatment options limited
- Data privacy restricted
- Missions vary in workload, stress
- Surgeons may record data differently
- Crew may be reluctant to report medical events

Generation of ISS Incidence Numbers – Immunology Scrub

- Crew weekly PMC records found within the EMR (Electronic Medical Record) were reviewed.
- Reported symptoms were evaluated for correlation to the listed adverse event categories.
- There could be multiple events for individual crewmembers. Events were not double scored into multiple categories.
- Data tabulated from 37 long-duration ISS crewmembers (Exp. 1-28/29; totals 16.63 person flight years)
- This data represents a standard epidemiological survey of the EMR, reports symptoms not diagnosis



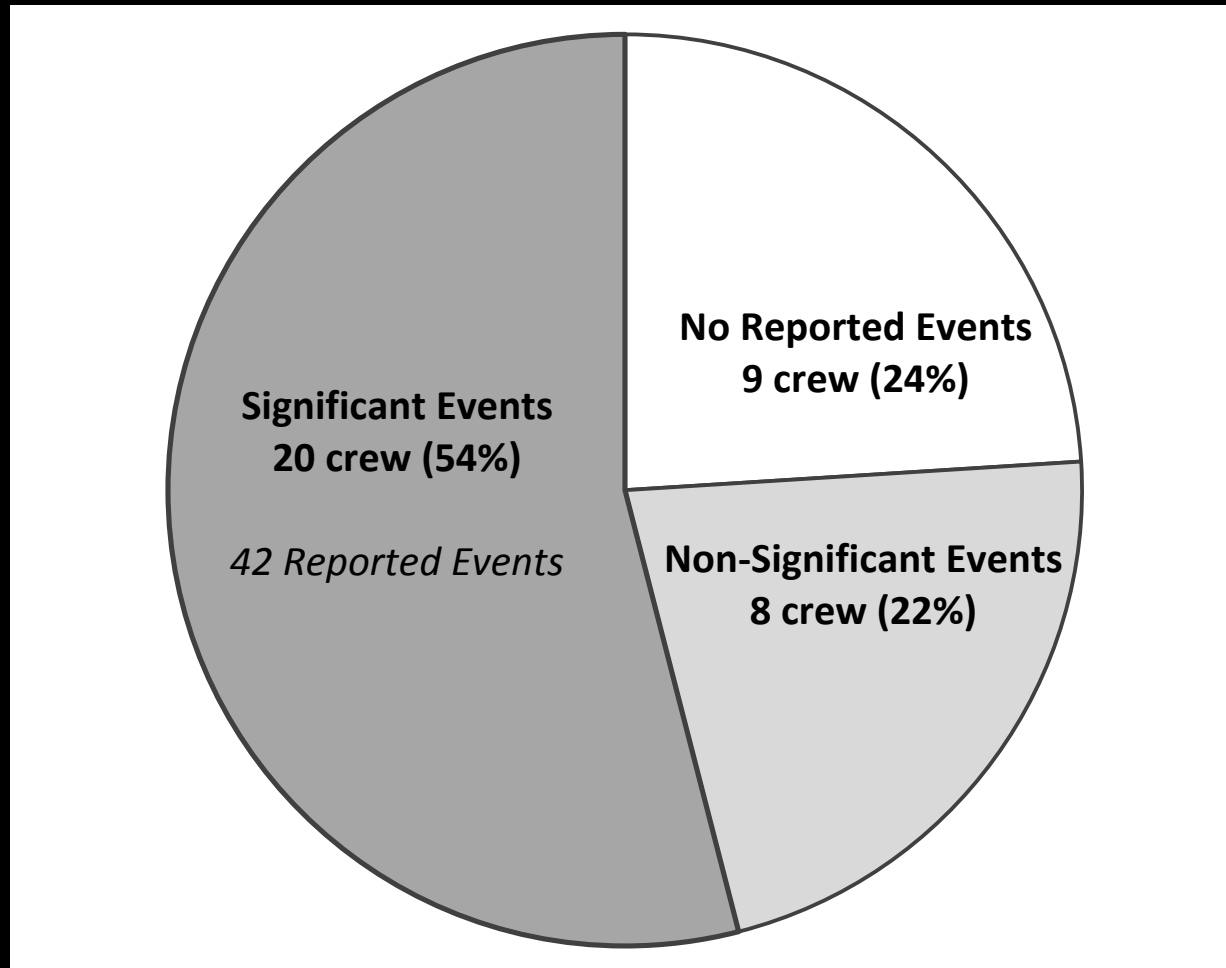
ISS Incidence Tabulation

Data tabulated from 37 long-duration ISS crewmembers
(Exp. 1-28/29; totals 16.63 person flight years)

| Medical Conditions | Total events | Events/ person year |
|--|--------------|------------------------|
| Allergic Reaction | 1 | 0.06 |
| Anaphylaxis | 0 | --- |
| Upper Respiratory Infection (combination of rhinitis, nasal stuffiness and sneezing) | 5 | 0.301 |
| Eye Infection | 0 | --- |
| Herpes Zoster | 5 | 0.301 |
| Otitis Media/Externa (ear pain, or ear stuffiness+congestion) | 17 | 1.022 |
| Pharyngitis (sore throat) | 1 | 0.06 |
| Sepsis | 0 | --- |
| Sinus Infection | 0 | --- |
| Skin Infection (including scalp pruritis, pus forming wounds on wrist, finger) | 5 | 0.301 |
| Skin Rash/Hypersensitivity (including skin conditions such as tinea versicolor, dermatitis, rosacea) | 23 | 1.383 |
| Urinary Tract Infection | 1 | 0.06 |
| Malignancies* | 0 | --- |
| Autoimmunity* | 0 | --- |
| Infections, Other* [#] | 11 | 0.666 |
| Total: | 69 | 4.18 |

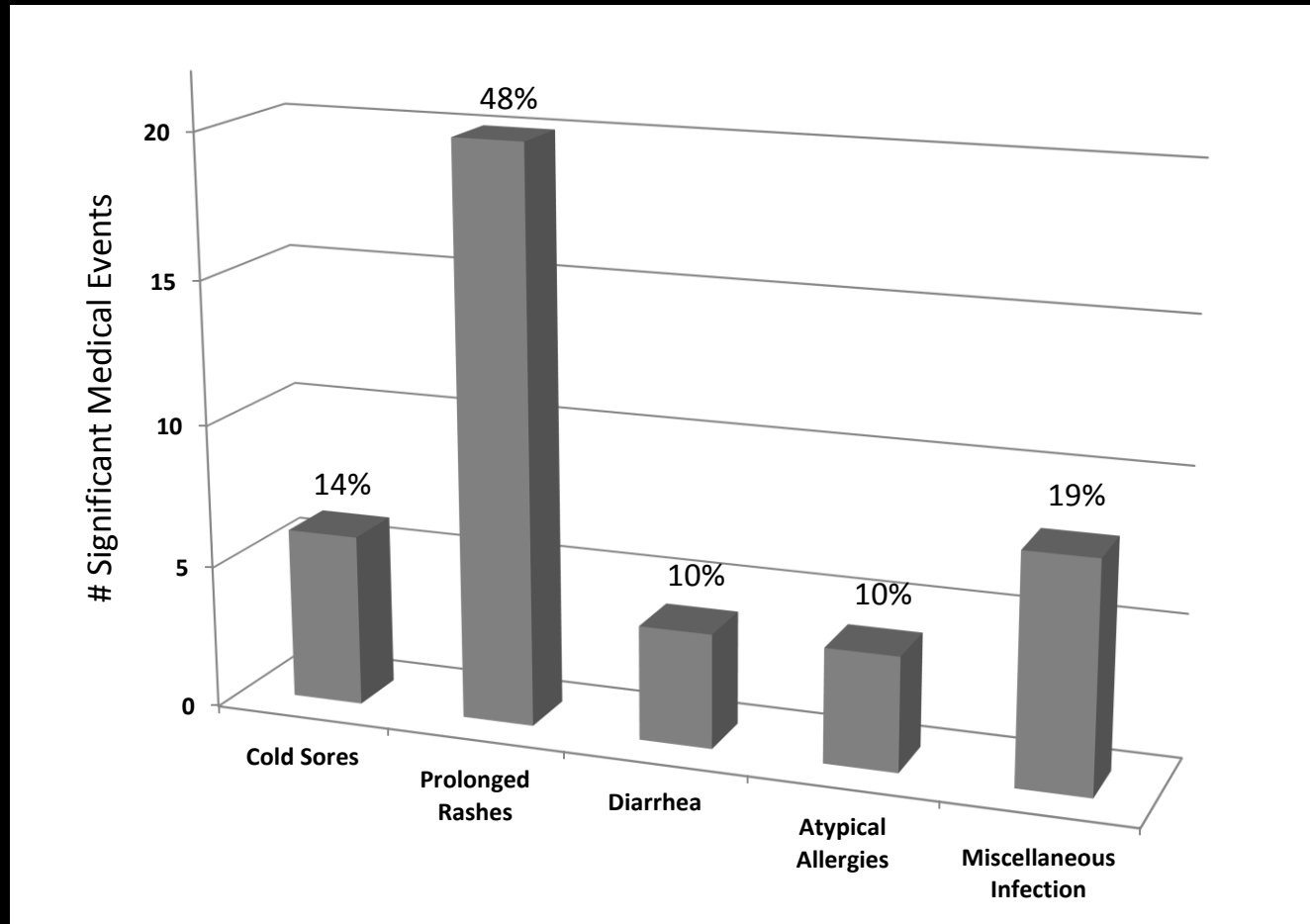
Additional Crew Incidence Observations

Breakdown of 69 in-flight medical events in the context of clinical significance: significant versus non-significant in 37 six-month ISS crew-missions.



Additional Crew Incidence Observations

Breakdown of 42 reported significant medical events reported in 20 of 37 ISS crewmembers. Relative percentages among the reported events are indicated.



Terrestrial Incidence of Skin Rashes

- Skin conditions account for 7% of out-patient visits to primary care providers in the U.S.
- In 2001, there were 37.9 visits to office-based dermatologists for skin conditions in the U.S. (0.136 visits/person-year)
- In 2001, there were 12.1 million visits to physician offices for skin rashes in the U.S. (0.044 visits/person-year)

References: -National Ambulatory Medical Care Survey: 2001 Summary
-U.S. Census Bureau, Statistical Abstract of the United States: 2001

Case Study ISS Astronaut

- Typical busy pre-mission training schedule
- Launch on Soyuz; docking to ISS + 2 days
- 191 day mission onboard ISS
- 3 Shuttle dockings, 2 Progress dockings, 1 ATV docking
- 5 EVA activities (12 Shuttle EVA)
- Typically busy mission schedule
- Landing on Soyuz, GCTC 1 week

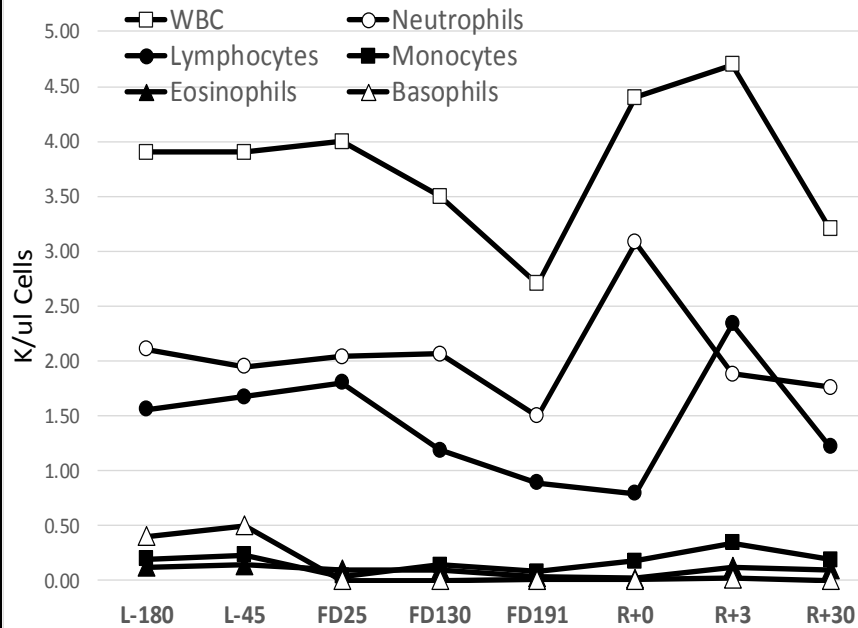


In-Flight Rash Image

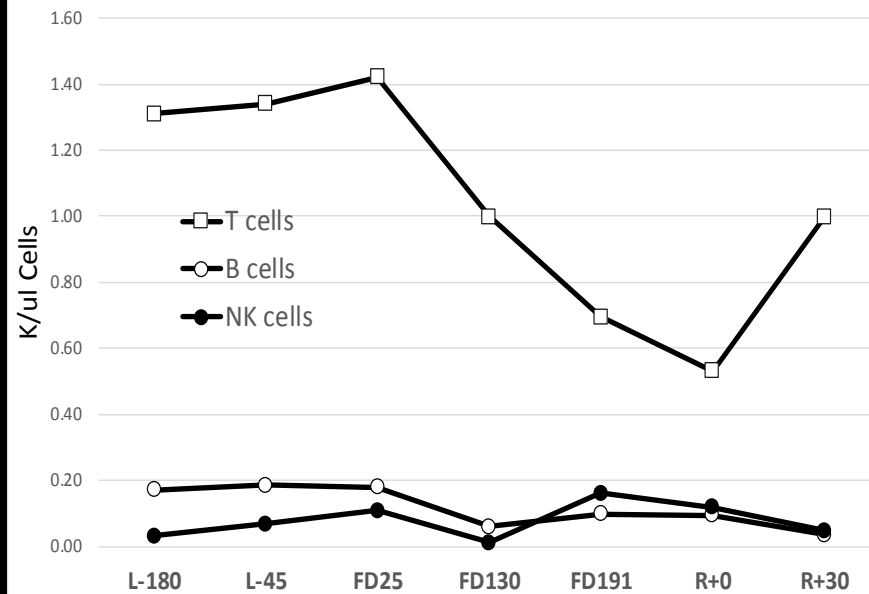


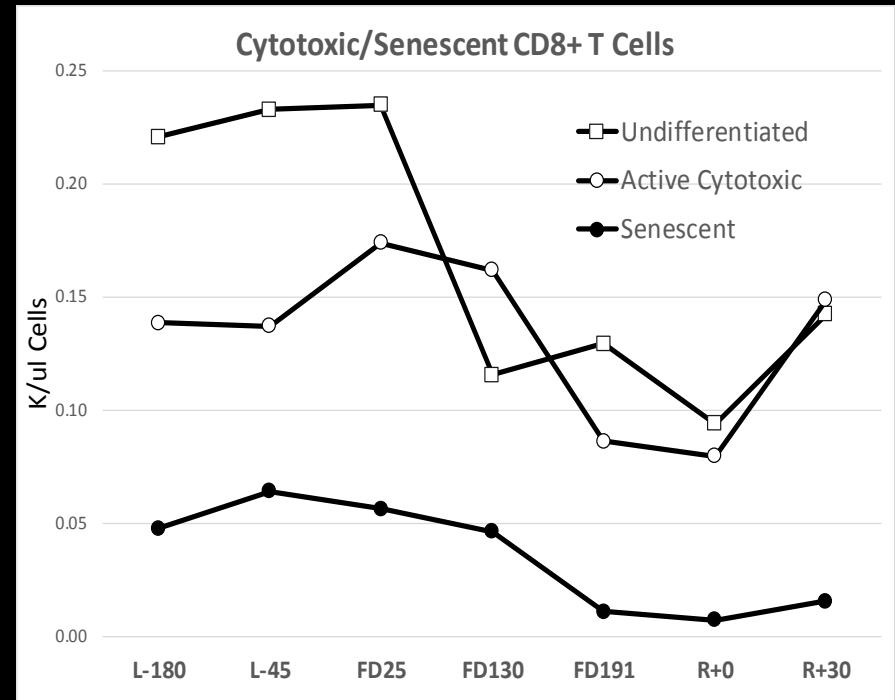
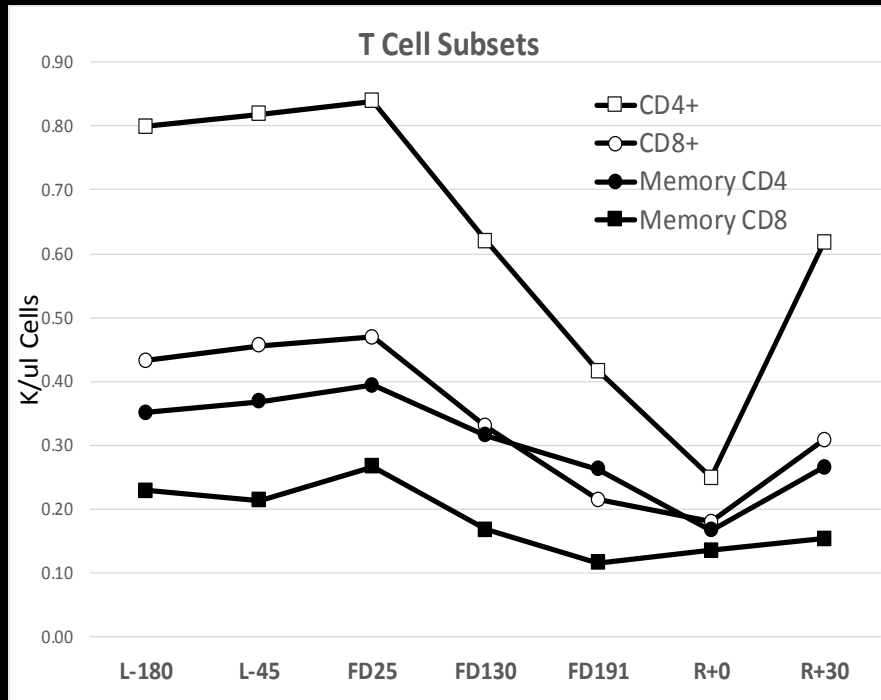
Peripheral Leukocyte Subsets

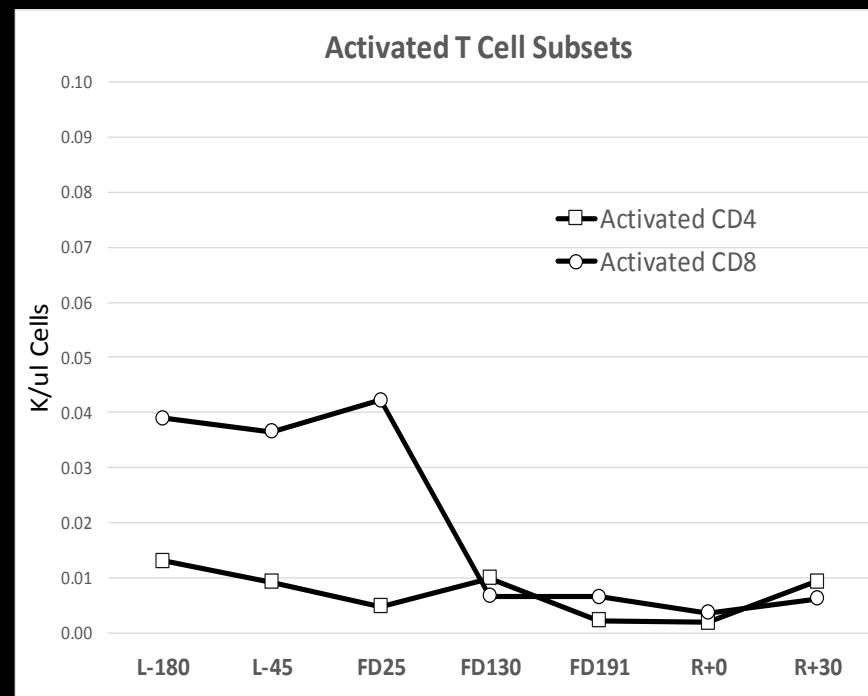
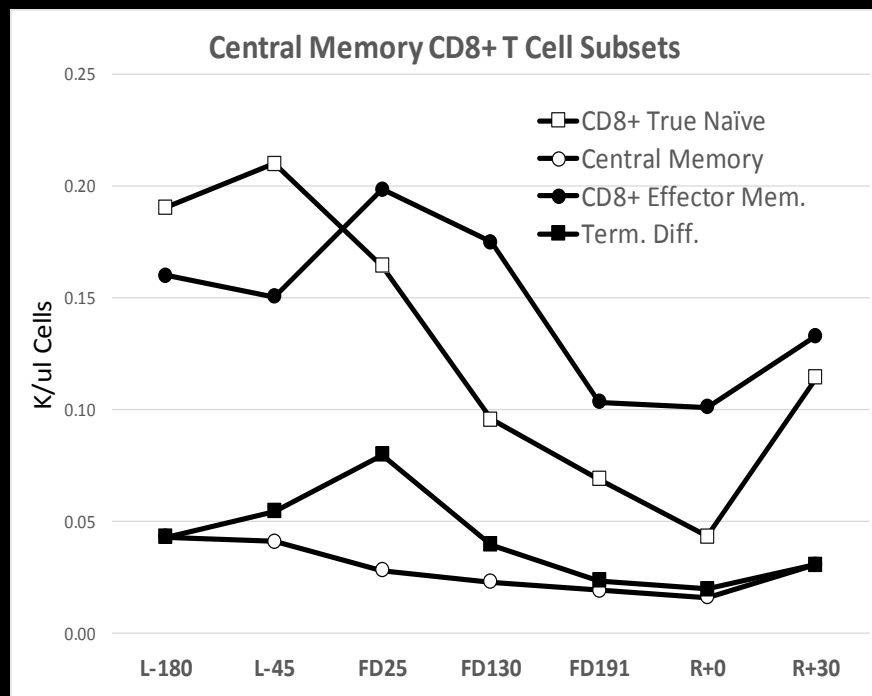
Bulk Leukocyte Subsets



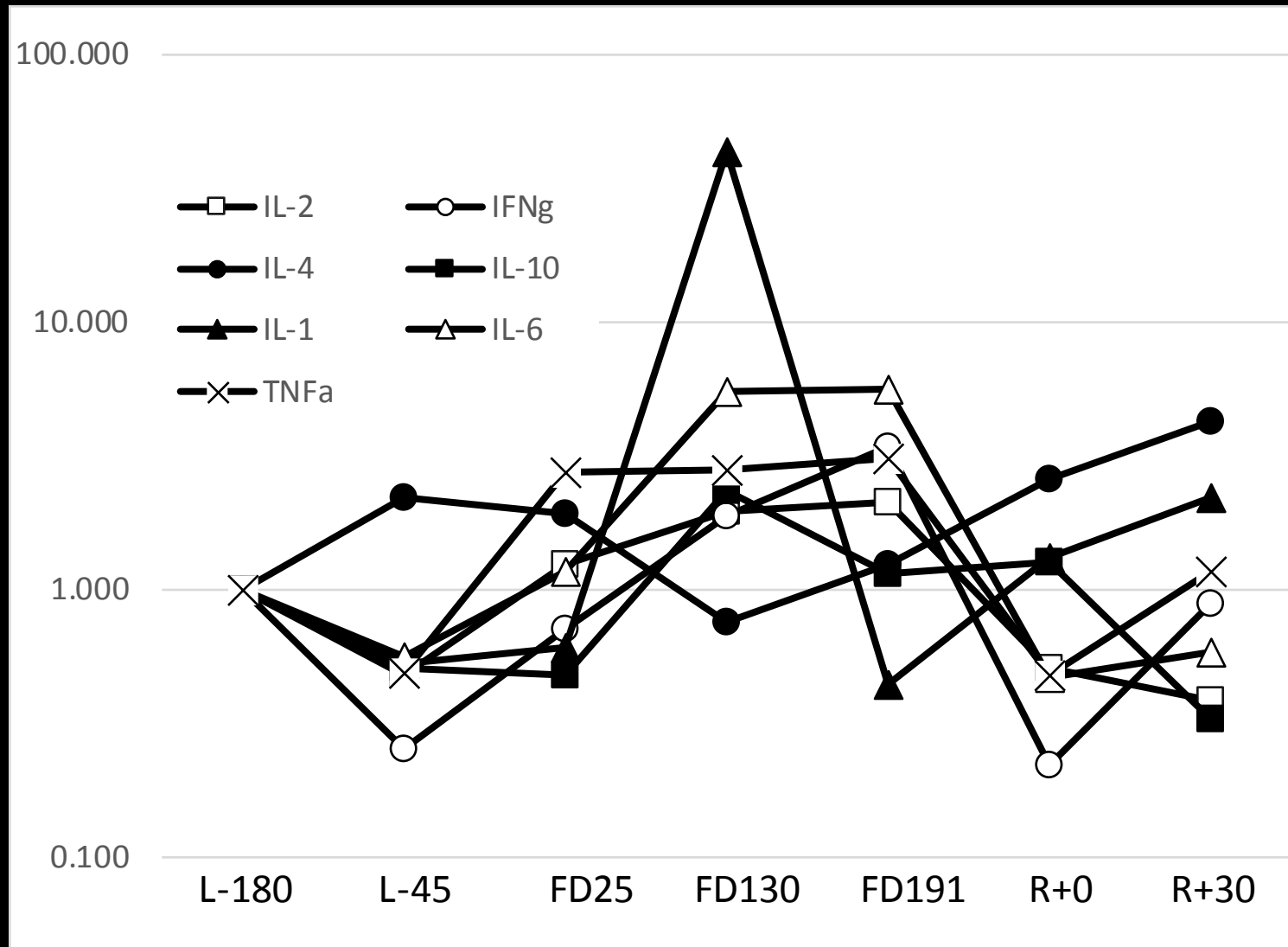
Lymphocyte Subsets



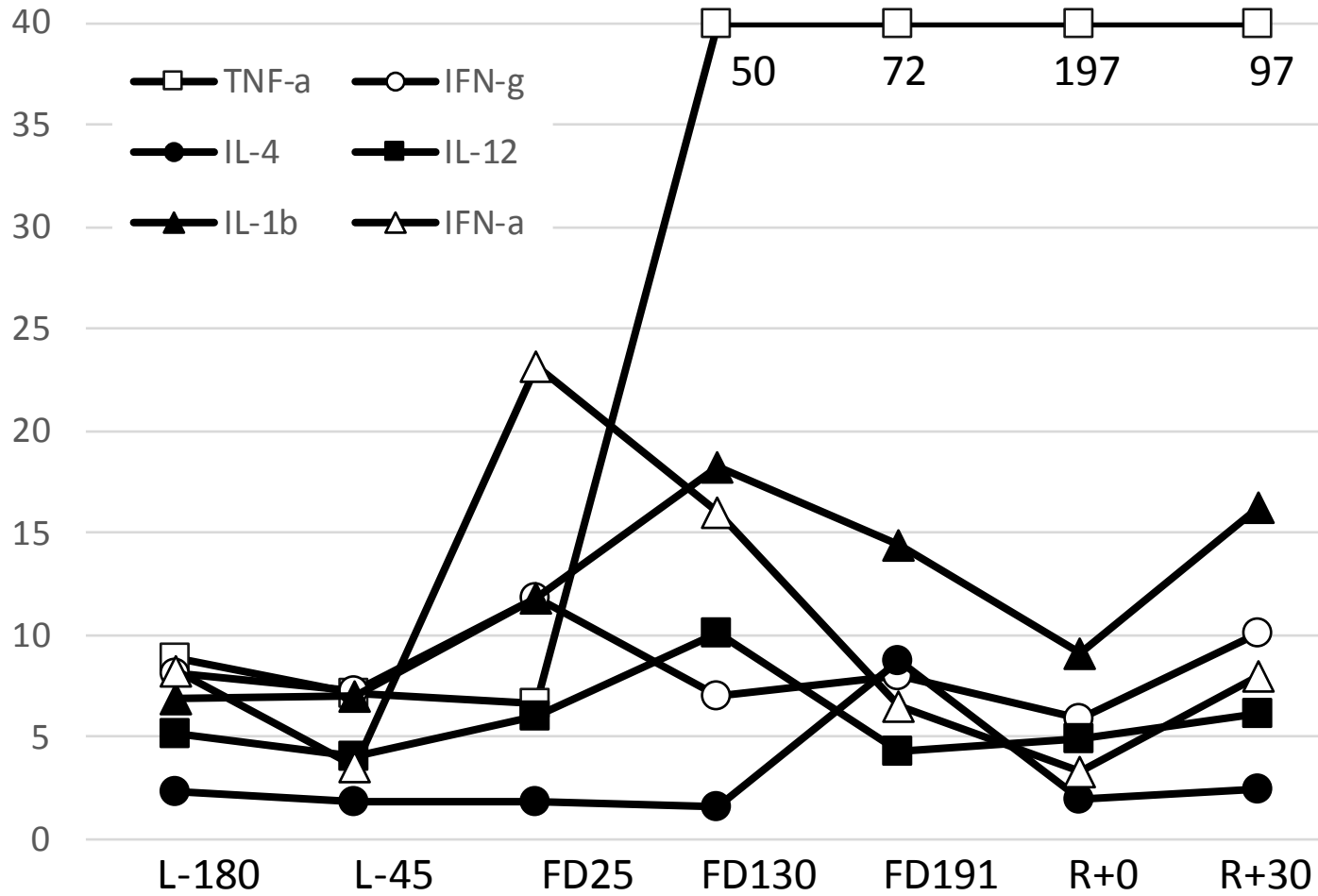




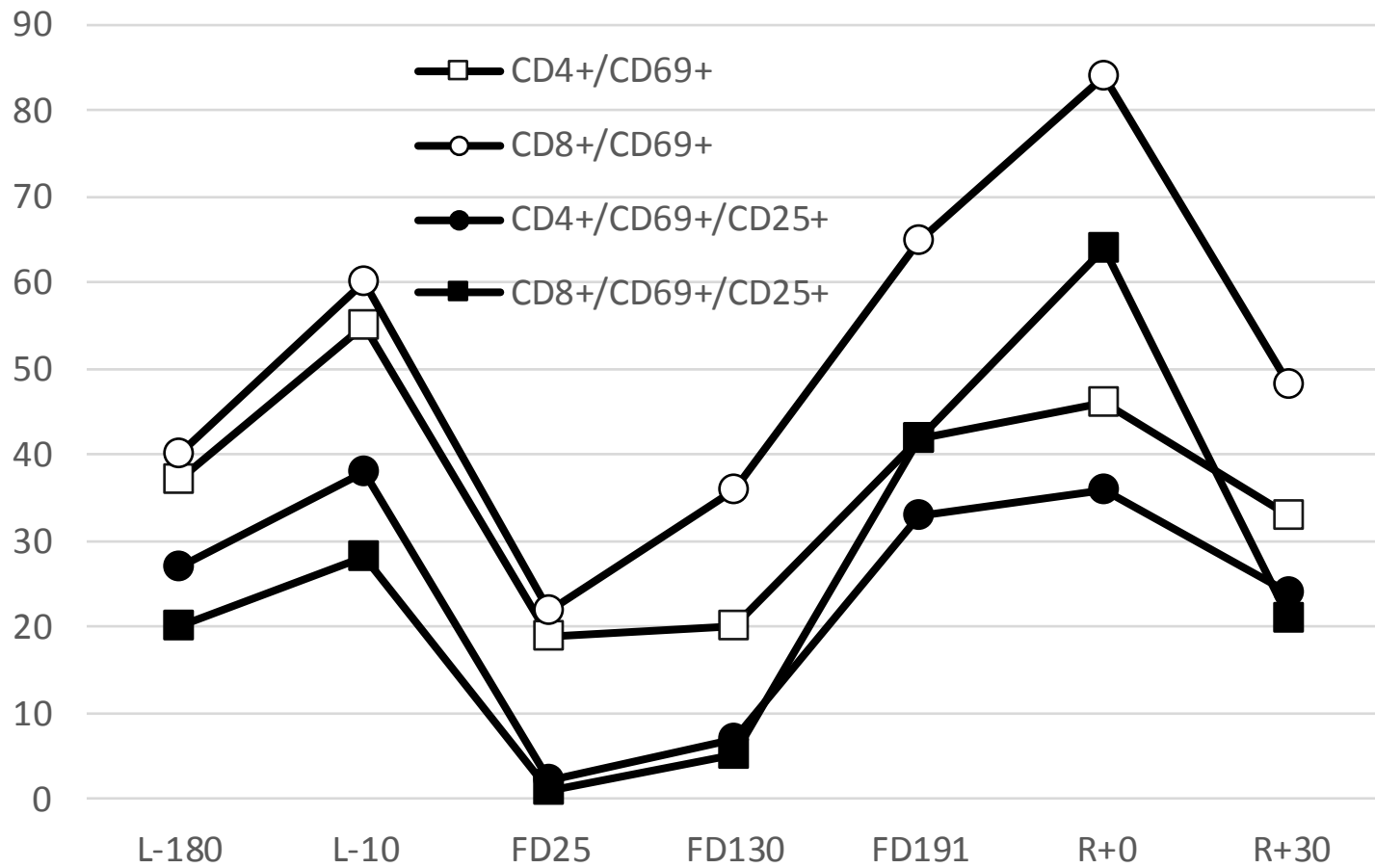
Peripheral Blood Cytokine mRNA Expression



Plasma Cytokine Profile

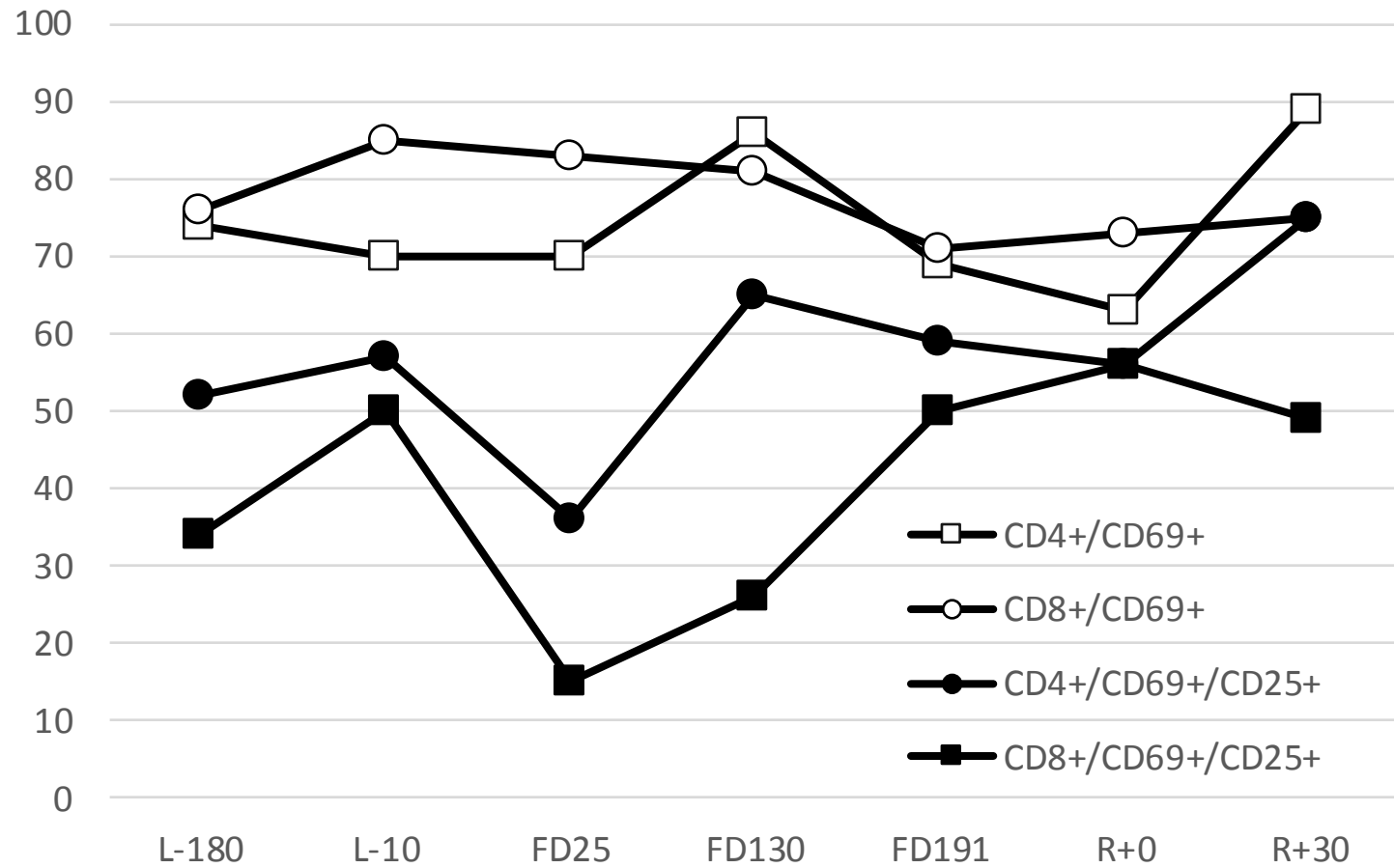


T Cell Function SEA+SEB (24hr)

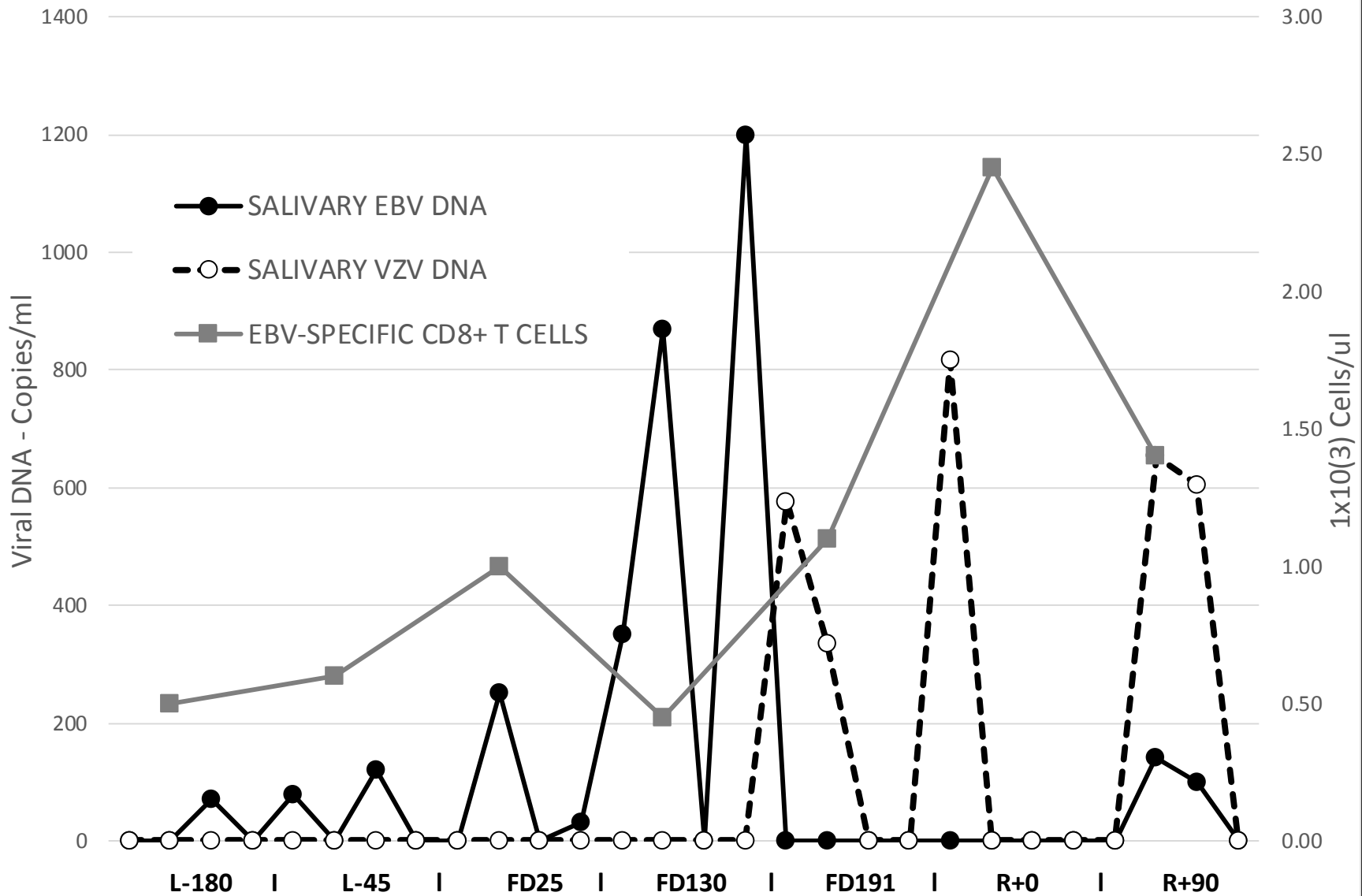


T Cell Function

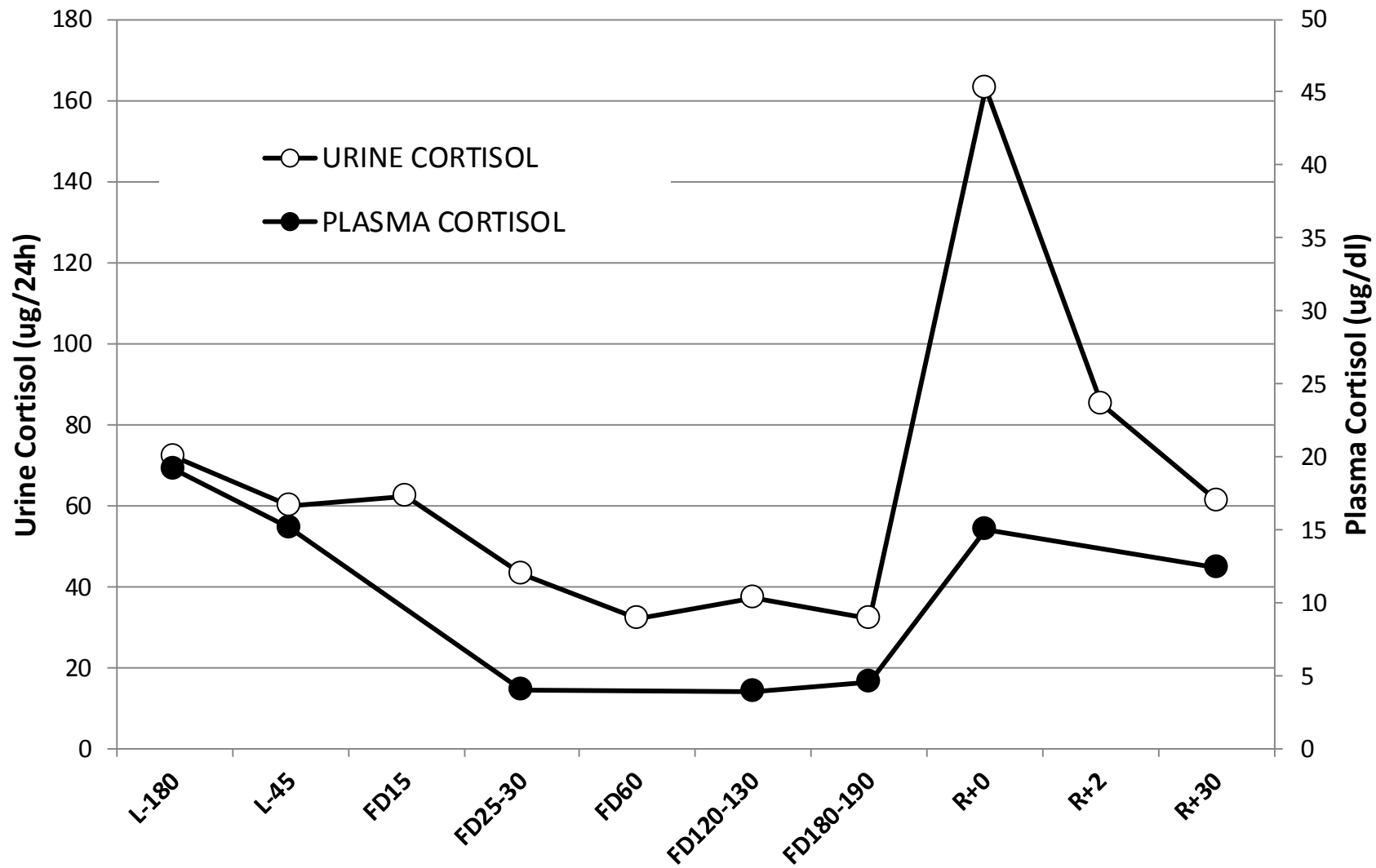
anti- CD3+CD28 (24hr)



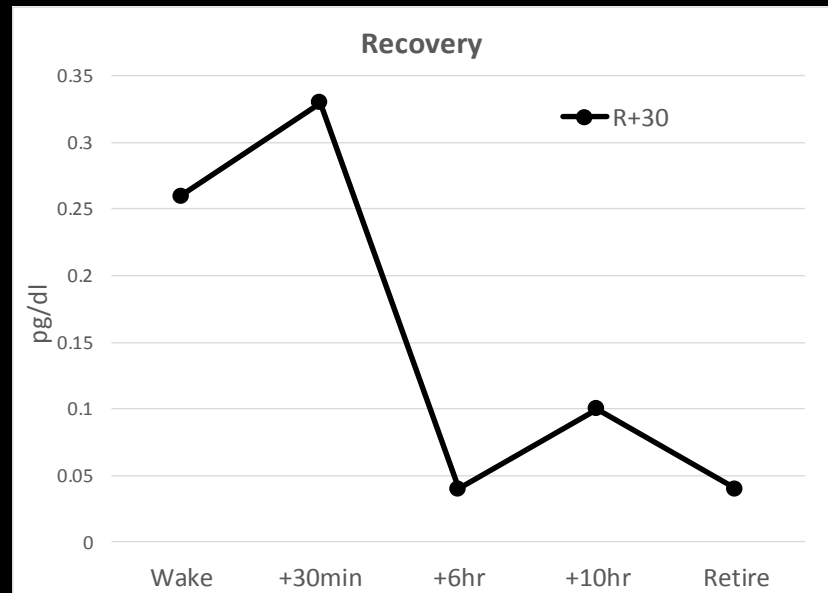
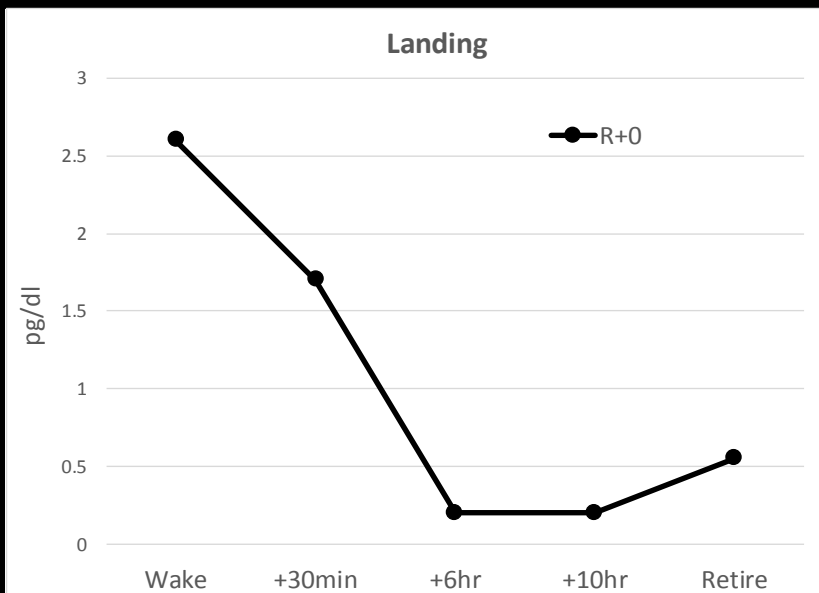
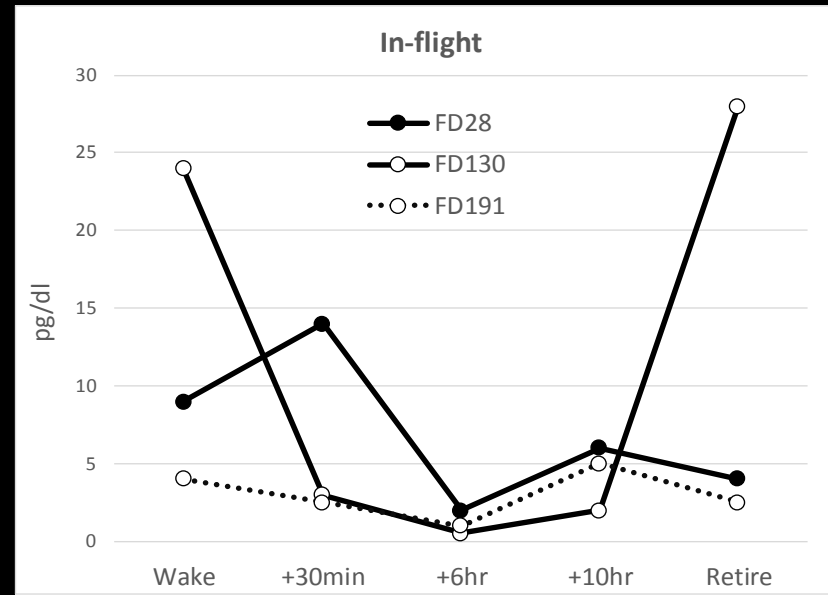
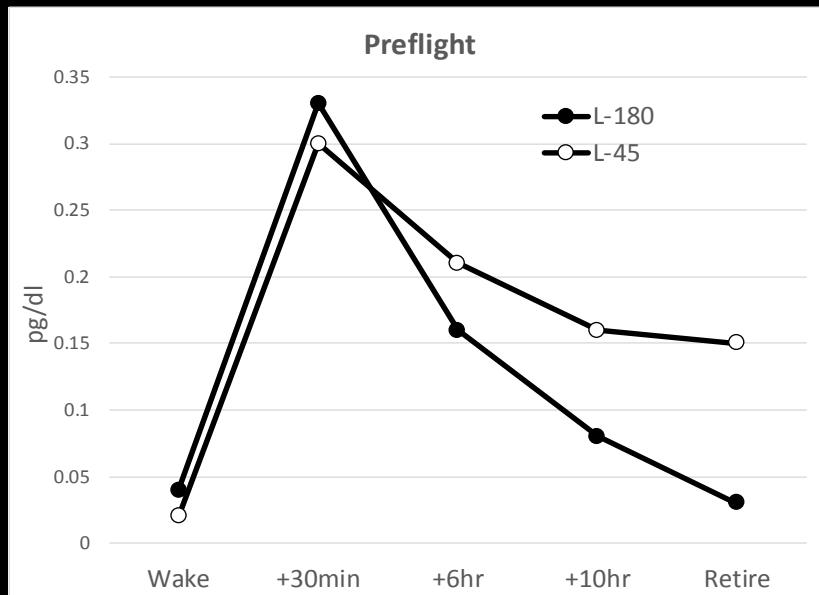
Latent Herpesvirus Reactivation; EBV Specific T Cells



Cortisol



Circadian Rhythm of Salivary Cortisol



Mitogen Stimulated Cytokine Profiles (pg/ml) anti-CD3+CD28 (48hr)

| | L-180 | L-45 | EAR | MID | LATE | R+0 | R+30 |
|-------|-------|-------|-------|-------|-------|-------|-------|
| IL-1b | 11828 | 16269 | 114 | 665 | 247 | 442 | 10918 |
| TNFa | 3651 | 5045 | 1319 | 1810 | 5382 | 2077 | 4405 |
| IL-6 | 8890 | 8673 | 2785 | 6301 | 8625 | 7005 | 8732 |
| IL-8 | 12165 | 11408 | 11708 | 12005 | 12131 | 12014 | 11706 |

Mitogen Stimulated Cytokine Profiles (pg/ml) anti-CD3+CD28 (48hr)

| | L-180 | L-45 | EAR | MID | LATE | R+0 | R+30 |
|----------|--------|--------|--------|--------|--------|--------|--------|
| IFNg | 1794 | 14610 | 912.36 | 341.64 | 5607 | 1936 | 13754 |
| IL-2 | 740.75 | 674.44 | 1479 | 865.92 | 370.83 | 109.96 | 1374 |
| IL-4 | 169.08 | 185.22 | 152.54 | 137.16 | 149.46 | 117.85 | 176.36 |
| IL-5 | 31.68 | 29.16 | 31.09 | 16.96 | 15.62 | 16.45 | 29.39 |
| IL-10 | 3163 | 3080 | 152.77 | 184.68 | 150.93 | 551.93 | 3377 |
| IL-12p70 | 5.85 | 7.48 | 3.89 | 2.38 | 22.97 | 3.24 | 8.13 |

Mitogen Stimulated Cytokine Profiles (pg/ml) anti-CD3+CD28 (48hr)

| | L-180 | L-45 | EAR | MID | LATE | R+0 | R+30 |
|--------|--------|--------|--------|--------|-------|--------|-------|
| IL-13 | 284.07 | 738.17 | 362.64 | 184.89 | 812.5 | 659.26 | 1543 |
| IL-7 | 25.81 | 21.27 | 20.23 | 23.19 | 25.81 | 23.63 | 25.71 |
| GM-CSF | 1092 | 985.34 | 686.15 | 986.86 | 1059 | 462.01 | 1645 |

Conclusions

- Spaceflight is associated with persistent immune system dysregulation and latent herpesvirus reactivation
- There is some degree of clinical incidence onboard ISS, with rashes among the most frequently reported symptomology
- Case study astronaut developed novel allergy symptoms and atopic eczema on mission day 17 and never fully resolved
- Supplies of anti-histamines and topical steroids were periodically exhausted
- Symptoms generally correlated with stressful mission events
- Case study subject displayed typical depressions in T cell function, cytokine dysregulation
- Case study subject shed EBV through mid-mission, and VZV late in-flight through R+30

Conclusions

- Spaceflight is a granular experience consisting of chronic stress interspersed with periodic acute stressors
- Immune dysregulation during flight appears to be polar, with some adaptive processes depressed (T cell function, HV shedding); whereas some innate processes are elevated (inflammation, hypersensitivity reactions)
- Exploration immune countermeasures must be considered carefully from among multisystem (exercise, etc.), benign supplements (probiotics, etc.) to pharmacological interventions (beta blockers, etc.)

